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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,243	07/16/2001	Alexander H. Taylor	P50770X1C1	4165

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,243	TAYLOR, ALEXANDER H.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44,48-62 and 64* is/are pending in the application.

4a) Of the above claim(s) *54-59 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44,48-53 and 60-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

LCT 1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/17/04*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

The request filed on 7/6/04 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/905,243 is acceptable and a RCE has been established. Claims 40-44, 48-62, 64 are pending. An action on the RCE follows.

1. Claim 40 has been amended.

2. Claims 40-44, 48-53 and 60-62 are under examination and will be examined to the extent the species of Pan troglodytes is the elected species of Old World apes.

3. Claims 54-59 and 64 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 40-44, 48, 51 under 35 U.S.C. 103(a) as being unpatentable over Adair et al (WO 91/09967, published 7/91, PTO-892, paper #6) and further in view of Vijh-Warrier et al (Molecular Immunology 32:1081-92, 1995, PTO-892, paper #6) and Queen et al (US Patent 5,693,762, with priority to at least 1990) is withdrawn in view of the new grounds of rejection.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 103

7. Claims 40-44, 48, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adair et al (WO 91/09967, published 7/91, PTO-892, paper #6) and further in view of Vijh-Warrier et al (Molecular Immunology 32:1081-92, 1995, PTO-892, paper #6) and Queen et al (US Patent 5,693,762, with priority to at least 1990) and Co et al (PNAS 88:2869-2873, 1991).

The claims recite a variable region comprising CDRs from a rodent and framework regions from Pan troglodytes wherein at least one CDR-contacting amino acid from the acceptor framework is replaced with a donor wherein the CDR-contacting residues contacts a CDR within the van der Waals radius of an antibody or a salt bridge or a hydrophobic interaction and at least one human constant region and the antibody has a specific binding avidity that is within three-fold of the donor antibody.

Adair et al teach methods of CDR grafting comprising acceptor framework and donor antigen binding regions of rodent antibodies (see abstract). Adair et al also teach non-CDR framework residues which contribute to antigen binding and CDR contacting residues (see pages 20-23) and replacing residues that influence CDR or antigen binding and those that are in a salt bridge (see page 21) and constant regions from humans (see page 12). Adair et al does not teach that the framework residues be from Pan troglodytes or replacing residues within van der Waals radius or hydrophobic interactions or affinity within three fold. This deficiency is made up for in the teachings of Vijh-Warrier and Queen et al and Co et al.

Vijh-Warrier et al teach the nucleotide and amino acid sequence of the variable region of a Pan troglodytes antibody (see abstract). Vijh-Warrier also teach several human germline variable region genes (see Figure 3, 4, and 5, and Table 1) and that chimpanzee mAbs are no more likely to elicit deleterious anti-immunoglobulin responses in humans than human mAbs (see page 1089).

Queen et al teach CDR grafting of donor CDRs onto human or humanized frameworks and replacing frameworks of the acceptor when within 3Å or residues influencing the van der Waal forces of a CDR residue or interacting in hydrophobic interactions with a CDR residue (see column 14, lines 26-50).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody comprising donor CDRs from a rodent species and acceptor framework residues from Pan troglodytes in view of Adair et al, Vijh-warrier et al and Queen et al.

Co et al teach CDR grafting of murine residues onto human frameworks and the affinity of the humanized antibody is equal or about 2-fold within the murine antibody (see page 2872).

One of ordinary skill in the art would have been motivated to and have a reasonable expectation of success to produce the claimed invention because Vijh-Warrier et al teach "these findings suggest that chimpanzee mAbs are no more likely to elicit deleterious anti-immunoglobulin responses in humans than are human mAbs" (see page 1089) and that the chimpanzee VH and Vk genes are no more divergent than the human genes. In addition, one of ordinary skill in the art would have been motivated to

produce the claimed invention because Adair et al teach donor CDRs from non-human species such as rodents (see abstract and page 8, lines 3-7) and Adair et al teach a method comprising retaining residues that are involved with antigen binding or contacting the CDRs or replacing solvent exposed framework residues (see pages 20-23, 38-39, and Figure 3). In addition, one of ordinary skill in the art would have been motivated to and have a reasonable expectation of success to produce the claimed invention because Queen et al teach CDR grafting and replacing acceptor residues with donor residues when the residue influences CDR presentation, antigen binding and the residues are within van der Waals distance or result in hydrophobic interactions. In addition, one of ordinary skill in the art would have been motivated to and have a reasonable expectation of success to produce the claimed invention because the CDR grafted antibody of Co was within 2-fold of the binding of the parent antibody and it would have been obvious to obtain the affinity of the parent antibody in the humanized antibody. Thus, it would have been prima facie obvious to have used the framework regions from a Pan troglodyte to produce the claimed antibody due to the high homology between human and Pan troglodytes immunoglobulin amino acid sequences and combine the teachings of Adair and Queen et al and Co et al who has produced antibodies with rodent CDRs and combine this with chimpanzee frameworks due to the high homology between chimpanzee mAbs and human mAbs as taught by Vijh-Warrier et al. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 5/17/04 has been carefully considured but is deemed not to be persuasive. The response states that Adair et al make no suggestion that making replacements in a non-human framework would have the same effect as replacing residues in a human framework and the data of Vijh-Warrier et al do not provide the skilled artisan with a reasonable expectation of success in producing an antibody with binding similar to rodent and comprising CDR from a rodent and frameworks from chimpanzee (see page 7 of response) and Vijh-Warrier et al does not mention antigen recognition and provides no suggestion that replacement in the acceptor framework will affect antigen binding (see page 8 of response). In response to this argument, it appears that applicant is arguing the references individually and in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response further states that applicants disagrees with Vijh-Warrier et al's assumption that homologous framework regions between species will necessarily result in a reduction in immunogenicity and cites Kuus-Reichel as providing evidence that humans have human anti-human responses to their own antibodies. In response to this argument, While the reference cites some potential problems there are numerous reports of humanized antibodies that have little or no HAHA responses, see Colnot et al (Cancer Immunol Immunother. 52:576-82, 2003 abstract, who teach no detectable HAHA response with bivatuzumab and Cobleigh et al (J of Clinical Oncology 17:2639-

2648, 1999) who teach only one out of 211 patents had any detectable antibodies against rhuMAb HER2 (see page 2645). The response further states that the CDRs of antibodies from chimpanzee and human are no more than 73% homologous and thus the skilled artisan might expect a human passively immunized with a chimpanzee antibody to develop anti-idiotypic antibodies (see page 8 of response). In response to this argument, when comparing sequences for humanization the art looks to framework regions not CDRs because the CDRs are for binding and would be expected to differ perhaps significantly from antibodies the bind two antigens. Thus, one would look to frameworks and Vihj-Warrier teach that frameworks are more homologous in human and chimpanzee (see page 1088-1089). The response then states that if the frameworks regions is not 100% homologous to human then a skilled artisan cannot reasonably expect that making amino acid changes in an Old World Ape framework will successfully have the same effect as making substitutions in human framework)see page 9 of response). In response to this argument, while one would probably make changes in the old world ape framework region, these changes would be similar to those made in the humanized antibodies and tested for binding because in the humanized versions or method residues are mutated to regain or obtain similar binding as the parent. Thus, one skill in the art would expect to alter residues and these would have a similar outcome as residues altered in the humanization methods.

The response further states that Vihj-Warrier et al does not present any binding data relating to the avidity of a fused antibody (see page 9 of response). In response to this argument, again the response seems to be arguing the reference alone and in

response to this Co et al clearly teaches reasons to determine the affinity and to obtain antibodies that have the same or within 2-fold of the parent antibody.

Thus it would be obvious that the frameworks that comprise the antigenic regions of the antibody or at least the majority would be replaced in a rodent as taught by Adair et al or Queen to reduce the immunogenicity in a human with chimpanzee frameworks which as taught by Vijh-Warrier et al are almost identical to human frameworks and still low in immunigenicity and obtain those antibodies that have affinity within three-fold ad taught by Co et al.

Conclusions

8. No Claims are allowed. Claims 49-50, 52-53, 60-62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832